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INFECTIOUS DISEASE REVIEW

Bioterrorism

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Because of the recent terrorist attacks in the United States there has been an increasing need for health care practitioners to have a fundamental knowledge in the agents of bioterrorism. Unlike traditional acts of overt terrorism, bioterrorism is covert. This means the effects of the attack will first be identified in the emergency department. This new threat, as evidenced by the recent exposures to anthrax, has illustrated the importance of physicians in diagnosing, treating, and educating patients on bioterrorism. The goal of this article is to set a framework for understanding the most important agents as designated by the CDC.

The CDC has categorized the many agents of bioterrorism into categories A, B, and C. The A agents are felt to be the easiest to disseminate, cause the highest mortality, and require special preparedness. B agents are felt to be second in priority, and C agents are emerging pathogens.[1] Category A agents include: smallpox, anthrax, botulism, tularemia, and viral hemorrhagic fever. Category B agents include: Q fever, brucellosis, glanders, alphivirus, and various food and waterborn pathogens. Category C agents are considered emerging and include: nipah virus, hantavirus, tick borne hemorrhagic fever, yellow fever, and multidrug resistant TB. The focus of this article is to review the various aspects of category A agents deemed important for the recognition of a bioterrorist threat.

Smallpox was once considered extinct and captured in a repository at the CDC and the Russian equivalent in Siberia. Kanatjan Alibekov (Ken Alibek), once a leading bioweaponer of the Soviet Union, defected in 1992 and stated that there were 20 tons of liquid small pox loaded in war heads pointed at US cities.[2] The concern is that with the fall of the Russian economy this stockpile would be open to the highest bidder. This concern has prompted the US government to launch an effort to produce small pox vaccine. Tommy Thompson, the government's Director of Health and Human Services, has stated publicly recently that there are currently 15.4 million doses of vaccine now, and hopefully 300 million doses will be ready by the end of 2002.

This poxivirus, a DNA virus also known as variola major is highly infectious. In 1796 Edward Jenner noted that cowpox could be used to vaccinate people from smallpox. The pathology of the disease has shown us it has a long incubation period.[3] After being exposed the virus incubates for up to 14 days. At the end of this incubation period the initial symptoms appear like the flu: fever, myalgia, and back pain. Within four days the pox rash appears on the face and travels from head to toe. There is a 30% case fatality that usually results from circulating immune complexes and secondary infection.

The disease is very infectious and spreads person-to-person, as well as with fomites. Should an outbreak be recognized we would expect a large quarantine with vaccination for those within the quarantine area.[4] The obvious risk is the ease in which smallpox could be delivered, and the large susceptibility to our population.

Anthrax has been weaponized for over 70 years. It is a large gram-positive rod that forms spores. The spores are hearty and can exist for up to 60 days in a fertile environment before converting to a vegetative (active) form. The bacteria carries two plasmids.[5] One encodes a capsule that prevents phagocytosis. The other plasmid encodes three proteins: a binding protein (protective antigen) that allows the two other proteins to enter susceptible cells (this is the target for the vaccine). The other two proteins are the lethal factor and the edema factor. Using the binding proteins these weapons enter macrophages and wreak havoc. The edema factor is an adenylate cyclase that disrupts water hemostasis. The lethal factor causes the cell to release secondary mediators of sepsis.

Although anthrax can infect the skin or GI tract, the pulmonary form is the bioterrorist threat. Traditionally known as wool sorters disease, this manifestation occurs when the victim breathes spores in the size range of 1-2 um with an ld50 of about 8000 spores.[8] The mean time from exposure to symptoms is about one week. Clinically pulmonary anthrax has two stages: initially flu symptoms for hours to days, then abrupt onset of fever and sepsis. The classic x-ray shows a widened mediastinum although effusions are also noted.

The CDC recommends cipro 500mg po bid, 15 mg/kg for children for 60 days.[7] Recovery is possible if the toxin burden is not too high. In monkeys exposed to aerosol concomonent use of vaccine with cipro has proven beneficial. There has recently been concern over a strain of anthrax that has a plasmid from Bacillis Cerus that has a different binding protein and escapes the vaccine.[8] There is no person-to-person transmission so masks are not required.

Plague is the disease caused by *Yersinia pestis*. Known as the Black Death that killed 20 million people in Europe. It is a zoonotic disease caused by the rat flea. As the flea is infected it develops an ileus. The flea bites and vomits in the rat. As large numbers of rats die they look for secondary hosts (humans).[9] The bite of an infected flea will cause bubonic plague. Small numbers of bubonic plague victims will become septic and develop pneumonic plague.

It is pneumonic plague that would be the terrorist threat. Until recently it was possible to buy pneumonic plague over the internet. The Bagwan Rajneesh, an Oregon cult that poisoned salad bars with salmonella had a supply in their germ lab.[9,10] The bacteria could be dropped as an aerosol or infected fleas could be dropped as was done during World War II by the Japanese Unit 731 in Manchuria, China.[11] The bacteria are ingested by macrophages and resist destruction. They cause a sepsis type syndrome. The appearance of previous healthy people with severe pneumonic consolidation and DIC is classic. Occasionally victims will also have a cervical bubo.

The vaccine was discontinued in 1999 because it only prevented bubonic plague. Our only defense is a quick diagnosis and therapy. The recommended therapy is streptomycin 1 gm IM bid (15 mg/kg).[11] The fatality rate is increased if therapy is started 24 hours after treatment. Because streptomycin is infrequently used in the United States gentamycin, doxycycline, and fluroquinolones are recommended as alternatives. All close contacts (within two meters) require post exposure prophylaxis, which consists of two weeks of doxycycline.

Botulism is a disease characterized by an acute afebrile symmetric descending paralysis that always begins in the bulbar musculature. The botulism toxin is secreted by the anaerobic bacteria *clostridium botulinum* and is one of the most lethal toxins known to man. One gram of crystalline toxin evenly dispersed could kill one million people.[12] Historically, the toxin has been used by the Japanese war unit during World War II. The germ warfare unit at Fort Detrick Maryland had refined the process of mass producing the toxin.[13] It is currently believed that Iraq has enough toxins to kill everyone on the earth many times over. United Nations weapons inspectors found botulism along with anthrax and aflatoxin in the heads of many Iraqi missiles after the Gulf War.

Each colony of *clostridum botulinum* can form one of six toxin types (A-F). Each toxin is antigenically different but work via the same mechanism. The toxin enters the neuromuscular junction and gets taken up by the presynaptic neuron. The toxin breaks down the apparatus that brings the acetylcholine filled vesicle to the exit point of the neuron. Thus, no neurotransmitter is released into the neuromuscular junction.

The paralysis is descending and can rapidly lead to respiratory arrest. Since the paralysis is descending it allows us to differentiate it from tick paralysis and Gullian Barre syndrome.[14] Currently, the only therapy is antitoxin. The antitoxin is antigen specific. Until recently only antitoxin for the most common types was available (A, B and E). An experimental heptavalent antitoxin (A-G) will soon be available.[12]

Tularemia was first described in 1911 as a plague-like illness in rodents.[15] It is named after Tulare, California where it was discovered. It is a small non-motile gram-negative coccobacillus, and can

enter the body via skin, GI or mucosa. It is a facultative intracellular organism that exists in the macrophage. The major target organs are the spleen, lungs, liver, and kidney. Granulomas form in these organs with central caseating necrosis, similar to Tuberculosis. The disease is endemic in animals and spread by ticks, mosquitoes, lice, flies, and ingestion of rodent excreta contaminated food. Backpackers in the high Sierra can acquire it from biting flies. Humans are accidental dead end hosts; there is no human-to-human transmission. The disease can have cutaneous ulceroglandular manifestations but aerosol inhalation causes the largest morbidity and mortality.

It has been suggested that it was used as a biological weapon during World War II on the Eastern Front.[15] The potential for use as a biological weapon was recognized by the United States and studied extensively at Fort Detrick.[13] As an aerosol in a biologic attack, we would see nonspecific febrile illness three to five days after exposure. Young people who have a common geographic factor and seem to have community acquired pneumonia with a high morbidity are suspicious for *francisella tularensis*. The earliest radiographic findings include peribronchial infiltrates advancing to bronchopneumonia in one or more lobes.

A live attenuated vaccine has been used for laboratory workers for years. Unfortunately, Tularemia, unlike smallpox and anthrax, has a very short incubation period, which makes post exposure vaccination less helpful. The preferred therapy is similar to plague with streptomycin as first line followed by gentamycin and doxycycline.[15] Close contacts are not recommended to receive antibiotics unless they entered a known contaminated area. Respiratory isolation is not recommended for Tularemia patients.

Viral Hemorrhagic Fever

The Viral Hemorrhagic fever is a clinical syndrome that results in profound internal bleeding. Several zoonotic viruses including filoviruses (Ebola and Marburg virus), Arenavirus family (Lassa virus and Argentine Hemorrhagic fever), bunyavirus (Hanta virus, CCF), and the Flavivirus family (Yellow fever and Denge HF).[16]

Humans are not the natural reservoir for any of these diseases. However, if accidental transmission to humans occurs, person-to-person transmission is possible. All of these diseases except Dengue fever can be infectious by aerosol or fomite from a sick person who is massively viremic

Not all patients who contract one of these viruses will exhibit features of viral hemorrhagic fever; it is a balance of host factors and viral strain. The target organ of these viruses is the vascular bed of various organs, thus the dominant features of the illness will be a consequence of vascular damage and permeability, i.e. rising liver function tests, proteinuria, leucopenia, and thrombocytopenia. The syndrome should be suspected in any individual who traveled to an infectious zone with evidence of vascular involvement, i.e. subnormal blood pressure, postural hypotension, petechiae, non-dependent edema, or flushed face.

Ebola is the one virus that has received the most press. Members of the Aum Shinrikyo cult that released serine gas in the Tokyo Subway attempted to fly to Zaire to acquire and weaponize the virus.[4] The reservoir is unknown, but believed to reside in bats. The symptoms begin within a few days of exposure and include fever headache, myalgia, diarrhea and a nonspecific rash. Within one week this progresses to chest pain, shock, and death. The case fatality is extremely high making it an effective weapon. An epidemic in the fall of 2000 killed hundreds of persons in Uganda. In December 2001, an epidemic occurred in Gabon.

Marburg is in the same family as Ebola. According to Ken Albeck, former bioweapons engineer of USSR, this virus has been studied, weaponized, and has killed members of the Russian military. It has a rather sudden onset with similar symptoms to Ebola. Five days later a macular papular rash emerges on the trunk. The case fatality is believed to be less than Ebola – approximately 20%. However, much less is known regarding the pathogensis, infectivity, and natural history in comparison to Ebola.

Summary: In these changing times of health care, it is easy to overlook many of these diseases. Developing nations see biologic weapons as an inexpensive way to become a global power. Many of these agents and some of the CDC B agents can be acquired not only by foreign terrorists, but domestic terrorists as well. Whatever the source of these microscopic killing machines one thing stands clear: health care practitioners, and most notably, Emergency Department physicians, will be at the forefront of the crisis.

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